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LUNG CANCER: EXECUTIVE SUMMARY

The smoking and health controversy remains unresolved, despite claims to the contrary. This is clearly demonstrated by the many still unanswered questions about the relationship between smoking and lung cancer. Without resolution of such gaps, it cannot be maintained that cigarette smoking has been proven to cause lung cancer.

The causal hypothesis regarding smoking and lung cancer is based mainly on population (epidemiological) studies in which smoking has been reported to be statistically associated with lung cancer mortality. Although such studies can provide a great deal of information and can identify many variables, such as smoking, diet, genetic predisposition, and occupational exposures, as risk factors for the development of the disease, statistical information alone can never establish causation. The role of statistics is to indicate areas for further investigation -- not to draw conclusions about scientific causation.

Furthermore, epidemiological studies have inherent limitations; they cannot adequately take into account the possible influence of various factors also associated with lung cancer development, such as the genetic backgrounds, the lifestyle choices (e.g., diet), and the environmental exposures (e.g., occupation) which vary among people, particularly among smokers and non-smokers.

Scientists have long recognized that these factors may be involved in disease development. Consequently, statistical reports on smoking and lung cancer which did not and frequently could not account for these factors are of limited value in establishing causation. As a scientist who believes smoking is involved with lung cancer has conceded, "It is clear that the riddle of smoking and lung cancer will continue to challenge the ingenuity of epidemiologists."[1]

Moreover, despite what is alleged about the statistics on smoking and health, some of the data do not support the claimed causal relationship. For example, if smoking causes lung cancer, why do the vast majority of even "heavy" smokers in the studies not develop lung cancer?[2] Also, under the causal theory, one should expect higher lung cancer death rates in countries where more cigarettes are smoked. However, this is not always the case as shown by the following examples which take into account the latency period or the number of years claimed to be required between exposure to cigarette smoking and the development of lung cancer. In the United Kingdom, where cigarette consumption was lower in 1930 than in the United States, lung cancer death rates in 1950 were higher. Also, Japan had higher consumption in 1930 than Germany, Spain and France, but much lower lung cancer death rates in 1950 than those three countries.[3] There are no data to suggest that this has changed in more recent years.

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Although hypotheses and theories appear frequently in the literature, no biological mechanisms have been presented to explain how cancer is caused, either by smoking or by any other factor. Hypotheses and theories are, by their very nature, speculative and unproven. In this regard, two scientists have commented, "Although a large number of factors have been associated with the development of malignant neoplasms [cancers] in humans, the mechanisms involved are still largely unknown."[4] Without knowledge of how an agent causes disease, one must conclude it is still a suspect, not an established cause.

The results of laboratory studies and animal experiments also have been inconclusive. Although thousands of laboratory animals have been exposed to whole fresh tobacco smoke, no animal inhalation experiment with fresh whole tobacco smoke has resulted in the production of human-type lung cancer.[5] Those who claim that cigarette smoking causes lung cancer have been unable to give a satisfactory explanation for this scientific gap in their chain of evidence.

In conclusion, the deficiencies and weaknesses in the data from the statistical studies and the laboratory investigations and animal experiments point out sharply how much more needs to be learned before the smoking and health controversy can be finally

resolved. Thus, despite the claims that are frequently made about smoking and health, it has not been scientifically established that smoking causes lung cancer.

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LUNG CANCER

Foremost among the charges against cigarette smoking is the claim that smoking causes lung cancer. Certainly, there are few, if any, who have not heard that claim. What has not been so well-publicized are the scientific data that are inconsistent with this claim and the vital questions that remain unanswered about the nature of the reported relationship between smoking and lung cancer.

Individuals making this assertion against smoking rely primarily on data from population (epidemiological) studies which have reported a statistical association between smoking and lung cancer. To say that there is a statistical association between a factor such as cigarette smoking and a disease such as lung cancer means that the factor, commonly referred to as a "risk factor," and the disease frequently occur together, or change together. However, it does not mean that a cause-and-effect relationship has been established. Thus, while epidemiological studies can identify risk factors such as smoking, diet, genetic predisposition, and occupational exposures, they cannot answer the important question of whether such associations have causal significance. Moreover, as many scientists have pointed out, demonstration of a biological mechanism and evidence from laboratory studies and animal experiments are needed to bridge the gap between reports of a statistical association and assertions of a causal relationship.

Without resolution of such gaps, it cannot be maintained that cigarette smoking has been proven to cause lung cancer.

Epidemiological Studies

The causal hypothesis regarding smoking and lung cancer is based mainly on epidemiological studies in which smoking has been reported to be statistically associated with lung cancer mortality. Epidemiological studies are primarily counting studies. Study subjects are divided into groups such as smokers and nonsmokers, deaths from certain specific diseases are counted, death rates are calculated, and comparisons of those death rates are made. It is apparent from this description that epidemiological studies do not in themselves address the biological mechanism for the disease studied.

There are two major types of epidemiological studies generally referred to in this context: retrospective and prospective. A retrospective study selects a group of people with lung cancer, usually hospital patients or hospital deaths, and then tries to go back in time through the use of questionnaires or records or interviews with relatives to collect information on their personal backgrounds, including their smoking histories. In one type of retrospective study, called a case-control study, the persons identified with the disease are compared to a group without the disease called controls. A prospective study identifies a group

of people without lung cancer, and, like a retrospective study, collects information on their personal backgrounds, including their smoking habits, but, unlike a retrospective study, follows them forward in time to observe any disease patterns they may develop. In both types of studies, the data collected are then arranged into various categories and statistical tests applied to determine if one group (smokers) differs from another (nonsmokers) with respect to a particular disease (lung cancer), and if that difference is related to any of the conditions, behaviors or other factors in the lives of the people in the study.

These statistical studies can provide a great deal of information, and perhaps that is why people have become accustomed to saying that statistics "prove" something. However, such epidemiological data alone cannot prove causation. Even the 1964 U.S. Surgeon General's Report on Smoking and Health (frequently referred to as the Terry Report) conceded:

> Statistical methods cannot establish proof of a causal relationship in an association. The causal significance of an association is a matter of judgment which goes beyond any statement of statistical probability.[1]

Statisticians have attempted to resolve this dilemma in a variety of ways. For example, in 1959, Sir Austin Bradford Hill, who is regarded as a pioneer in the field of medical statistics,

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proposed nine criteria which he suggested should be considered before deciding whether a statistical association might be causal. However, after a lengthy discussion of these criteria, he conceded that "None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non."[2]

The authors of the 1964 Surgeon General's Report set out their own criteria for determining whether the reported association between smoking and certain diseases might be causal. These criteria have been utilized in the subsequent reports from the Surgeon General's office, including the 1982 report which focused exclusively on cancer. However, the application of the criteria to the epidemiologic data on smoking and lung cancer has also raised questions. For example, following the publication of the 1982 report, the late Philip R.J. Burch, an eminent medical physicist from the United Kingdom's University of Leeds, contended that an analysis of the epidemiologic data "show that not one of the criteria, plausibly interpreted, is satisfied by the epidemiologic evidence for lung cancer."[3] He specifically noted that even though the relative risk ratios for lung cancer mortality for 35 retrospective studies published during the period 1939-1970 and listed in the 1982 report tend to be greater for smokers than nonsmokers, they cover a very wide range, from 1.2 to 36.0 for men and from 0.2 to 5.3 for women. He also noted that similar data

were reported for the eight prospective studies listed in the report. For those studies, the mortality ratios (cigarette smokers vs. nonsmokers) ranged from 3.76 to 14.2 in males and from 2.03 to 5.0 in females. Professor Burch stated, "With ratios showing a range, overall, of more than two orders of magnitude it is not self-evident that any acceptable criterion of consistency has been satisfied."[4]

Professor Burch also pointed out anomalies in the "dose-response" relationship reported in several of the prospective studies. When he analyzed the relative risk of lung cancer -- for onset in British male doctors and death in Japanese males -- as a function of the daily amount of cigarettes smoked, he noted that the calculated risk between the two groups for the same amount smoked differed tremendously:

> At first sight, the sheer magnitude of the differences is the most astonishing feature, the relative risk at 38 cigarettes a day being just over 50 for the British doctors and around 5 in Japanese males. A factor of 10 is not readily explained away in 'causal' terms and (small) adjustments for the duration of smoking, etc.[5]

Based on such observations, it is apparent that statistics can only indicate the likelihood that any observed disease patterns are not caused by chance and point to areas for further investigation. As a distinguished American medical statistician once noted:

> The cause of cancer is fundamentally not a statistical question, but a biologic one. Statistics, if critically and carefully used, can provide useful 'leads,' but the definitive investigations must come from the biologic sciences, pathology, pharmacology, chemistry and so forth. All of them together must be brought to bear on the problem, if we are to answer the specific question at hand, and the many other questions that are involved.[6]

Moreover, epidemiological studies have inherent limitations. For example, smokers are a self-selected group, which means that they differ from nonsmokers in many ways besides their smoking habits. These include differences in lifestyle, characteristics and behaviors, such as eating habits and exercise patterns. Therefore, comparisons of smokers and nonsmokers made without regard for other differences are subject to scientific criticism. Nor can epidemiological studies adequately take into account the possible influence of such factors as occupational exposures, inherited tendencies to develop certain diseases, and many other biological and behavioral unknowns. Scientists have long recognized that these factors may also be involved in disease development. Consequently, statistical reports on smoking which do not and frequently cannot account for these factors are of limited value in establishing causation. A scientist who personally believes smoking is involved with lung cancer has conceded "it is clear that the riddle of smoking and lung cancer will continue to challenge the ingenuity of epidemiologists."[7]

Inconsistencies in the Epidemiological Studies

Many inconsistencies which raise questions about a causal relationship between smoking and lung cancer have been noted in the epidemiological studies. While the precise meaning of these inconsistencies may be unclear, they show that the case against smoking is not as simple as many people would like to believe.

For example, reports that lung cancer was starting to increase began to appear in the scientific literature before the marked increase in the popularity of cigarette smoking.[8] A medical doctor who studied these issues noted that English and French physicians were describing the clinical and pathological manifestations of lung cancer in medical journals more than 150 years ago, and that during the latter half of the 19th century, a great number of cases were reported in England, France, Germany and the United States. As he observed, "All this took place a long, long time before cigarette smoking became popular."[9]

There are other inconsistencies. For example, if smoking causes lung cancer, it would be reasonable to expect higher lung cancer rates in countries where more cigarettes are smoked. But that is not always the case, as shown by the following examples which take into account the latency period or the number of years

claimed to be required before cigarette smoking leads to the development of lung cancer, generally about 20 to 30 years. In Great Britain, for example, where cigarette consumption was lower in 1930 than in the United States, lung cancer death rates in 1950 were much higher than in the U.S. On the other hand, in Japan, where cigarette consumption was higher in 1950 than in Germany, Spain and France, lung cancer death rates in 1970 were much lower than in those three countries.[10] There are no data to suggest that this has changed in more recent years.

Also, if smoking causes lung cancer, why do the vast majority of even "heavy" smokers in the epidemiological studies not develop lung cancer?[11] Moreover, the same type of epidemiological information used to suggest that lung cancer has increased in smokers suggests that it may also have increased in nonsmokers.[12]

Furthermore, if smoking causes lung cancer, one would expect that the earlier a person starts to smoke and the more he smokes, the sooner he would get lung cancer. Yet nonsmokers and smokers (whether they smoke a little or a lot) all appear to develop the disease at about the same average age.[13] According to one expert: "That both the age of starting to smoke, and the rate of smoking, should have no appreciable influence on the average age

of onset of lung cancer greatly taxes, if it does not destroy, any causal hypothesis."[14]

In addition, if smoking causes lung cancer, it would seem unlikely that there would be large differences in lung cancer rates among different races or ethnic groups and between men and women, regardless of their smoking habits. However, it has been reported that there were fewer cases of lung cancer among Chinese and Japanese women living in Hawaii who smoked than among Hawaiian women who smoked.[15] It has also been reported that women in Hong Kong have a very high rate of lung cancer compared to women in other countries but that they smoke less.[16] In contrast, women in most other countries have lower rates of lung cancer than men, even if they smoke the same amount.[17]

Moreover, if smoking caused lung cancer, smokers who inhale cigarette smoke would presumably have higher rates of lung cancer than those who do not inhale. However, in some studies, lower lung cancer rates have been reported among inhalers than among noninhalers.[18]

There are other reported observations of a similar nature which appear inconsistent with the causal hypothesis. For example, although inhaled cigarette smoke is distributed equally between both lungs, lung cancers very rarely occur simultaneously in both lungs.

Similarly, cancer rarely occurs in the trachea (the "windpipe"), even though this organ is exposed to more tobacco smoke than either lung, because all the smoke going to the lungs passes through it. Likewise, there has been little change in the incidence of laryngeal cancer over the past decades, even though tobacco smoke also must pass through the larynx (the "voicebox") on its way to the lungs.[19]

Such inconsistencies in the epidemiological studies raise serious questions about the causal hypothesis.

Increased Mortality - Real or Apparent?

In recent years, there have been reports of a so-called "epidemic" increase in lung cancer deaths. Some point to this "epidemic" and simultaneous increases in the number of people who smoke as "proof" that smoking causes lung cancer. They find this simplistic explanation appealing, but is it supported by the data? A review of the scientific literature suggests that numerous concerns have been expressed about the reliability of such data. At the very least, such concerns should prompt further serious consideration before attempts are made to answer this question.

Diagnostic Problems

Many scientists have noted that the apparent increase in lung cancer may well reflect a greater ability to detect lung cancer rather than actual increases in the disease itself. They speculate that many lung cancer cases were never discovered in the years before more sophisticated diagnostic techniques were available; that is, lung cancer was underdiagnosed over a long period of time. Many of these same scientists believe that this improved diagnostic capability has been accompanied by another type of diagnostic error, the tendency toward overdiagnosis. In other words, primary lung cancer may now be diagnosed in patients who do not have the disease.

These scientists also believe they know how the tendency toward underdiagnosis may have occurred. Before the middle of this century, doctors were limited in their ability to detect lung cancer because they lacked the principal diagnostic methods -- x-ray, bronchoscopy, and sputum cytology -- now being used. One researcher, who studied the impact of these developments, has observed:

> The prodigious increase in lung cancer during the past three decades is not due to the exposure of the population to an alleged carcinogen but is the natural consequence of the widespread use of techniques not previously available.[20]

Radically improved techniques in more recent years, such as fiberoptic bronchoscopy, mediastinoscopy, computed tomography (CT), and magnetic resonance imaging (MRI), may also have contributed to reported increases in lung cancer.[21]

Support for the hypothesis that the "epidemic" may in part reflect dramatic medical progress can also be found in an examination of non-cancerous lung disease trends. For example, in 1900, the combined crude death rate for respiratory diseases in the United States exceeded 450 per 100,000, but there were no death rates recorded for lung cancer.[22] It has been estimated that if only a very small percentage of the cases diagnosed as tuberculosis or other infectious respiratory diseases were actually lung cancer, there would have been relatively little increase in the prevalence of this disease during the first half of this century. More specifically, one researcher has speculated that if only five percent of the deaths attributed to tuberculosis and other respiratory diseases among males over 35 years of age during that period had been lung cancer, it "would have resulted in a twofold lung cancer mortality increase between 1914 and 1950, instead of the recorded 26-fold increase." Likewise, he speculated that if only three per cent of the cases certified as dying of respiratory diseases had actually died of lung cancer, "the increase would have tripled." As he pointed out, "Experienced clinicians will find

little difficulty in postulating an error of 10 or 20 per cent in the clinical diagnosis of bronchogenic carcinoma, particularly, in an era devoid of x-ray examination, bronchoscopy, thoracotomy, and cytology."[23] Interestingly, recent studies have shown that lung cancer is still being confused with diseases such as tuberculosis, pneumonia and bronchitis.[24]

The theory that lung cancer has been overdiagnosed in recent years is supported by the results of studies comparing clinicians' diagnoses of lung cancer with autopsy findings of actual causes of death. Such studies have consistently reported large discrepancies. One chest specialist, using microscopic techniques, could confirm only 44 percent of the cases diagnosed by the clinicians as lung cancer.[25] He observed that a large part of the difficulty appeared to revolve around the clinician's opinion about the cancer's site of origin. Apparently, the overdiagnosis often occurs because the clinician classifies a lung cancer as primary, or originating in the lung, when in fact the cancer originated elsewhere and then metastasized or spread to the lung to cause a secondary, or metastatic, cancer. Without more detailed study, it is often impossible for the clinician to know that this occurred.

Yet another diagnostic phenomenon called "detection bias" may also be distorting the epidemiological picture regarding smoking and lung cancer. Detection bias occurs when a disease is diagnos-

tically sought more vigorously in people who are exposed to the suspected cause than in people without such exposure. That is, smokers are more likely to be given more diagnostic tests for lung cancer and, therefore, to be diagnosed with the disease than nonsmokers. A medical university research group confirmed its suspicion that such a bias may occur when it analyzed materials from populations of living and deceased patients and determined that lung cancers are less likely to be detected in certain groups of individuals, including nonsmokers.[26] The group asserted that its findings "indicate the scientific desirability of a reevaluation" of the reported association between cigarette smoking and lung cancer, "using newer epidemiologic methods that can compensate for the impact of detection bias in observational research."[27]

In summary, as a U.K. medical physicist has stated, diagnostic error may be largely responsible for the reported increases in lung cancer:

> Post-mortem studies of the frequency of lung cancer show that the most important factor in the increase of recorded lung cancer has been clinical diagnostic error. Severe underdiagnosis during the earlier part of the century was eventually followed, in the past decade or so, by overdiagnosis.[28]

Death Certificates

Another problem involved in assessing reports of an "epidemic" increase in lung cancer and its relationship to cigarette smoking is the type of data researchers rely on to describe large-scale mortality patterns. Most of the data are taken from death certificates. However, studies conducted to determine whether death certificates accurately reflect the actual cause of death have determined that such data may contain many errors. In fact, one researcher asserts that this information is "notoriously inaccurate."[29]

Errors in death certificate information have been chiefly attributed either to misdiagnosis or to recording errors. Errors related to misdiagnosis occur if the physician incorrectly diagnosed the patient's final disease and that inaccurate information is then entered on the death certificate. This occurs because the physician's diagnosis, usually found in the clinical or hospital record, generally serves as a basis for the cause of death listed on the death certificate unless it is corrected on the basis of laboratory or autopsy results.

Studies utilizing autopsy findings to evaluate the accuracy of clinical diagnoses have reported finding a high rate of error. In those studies, scientists have compared the results

of autopsies, which are considered the best and most reliable source of information on cause of death, with the causes of death listed on the death certificates. Such studies have consistently reported serious error rates between major clinical and autopsy diagnoses, ranging from 20 to 40 percent. Some have even reported error rates up to 60 percent.[30]

Of the various cancer sites analyzed in such studies, the lung frequently has received special attention from investigators interested in questions of diagnostic accuracy. Their research findings, while differing in some respects, have been consistent on one point: the rate of misdiagnosis of lung cancer has been high. Yet there seemed to be no consistent patterns or obvious explanations for the discrepancies.

Studies have reported that lung cancer has either been overdiagnosed (cases diagnosed as lung cancer turned out to be something else) or underdiagnosed (cases diagnosed as something else turned out to be lung cancer). In one study of 493 cancer cases in a New York City hospital, for example, more than 50 percent of the clinical diagnoses of lung cancer were reportedly found to be incorrect at autopsy.[31] Conversely, a Boston hospital study reportedly found that a large number of lung cancer cases had been missed clinically. Of the lung cancers confirmed at autopsy, 27 percent had not been diagnosed in the hospital.[32] Other studies

from countries as diverse as Israel,[33] Finland,[34] Scotland,[35] and the United States[36] have also reported varying rates of overdiagnosis and underdiagnosis of lung cancer.

The second major source of errors in death certificate information occurs if the physician makes the correct clinical diagnosis, but it is not properly recorded on the death certificate. In 1979, for example, U.S. researchers compared the hospital diagnosis for nearly 10,000 deaths with the underlying cause of death recorded on the death certificate. They reported finding differences in nearly 30 percent of the cases.[37]

Various theories have been advanced for such recording errors. It has been suggested, for example, that many physicians may not regard accuracy in death certificate information as an important concern. One pathologist commented that many physicians regard the death certificate as "a document which simply declares that the death was due to natural causes and [which] does not have medico-legal significance." He also noted that "doctors certifying deaths often fail to realise that the information they record is utilised by the statistician for compiling data of epidemiological significance."[38] Although physicians may not regard accuracy in recording death certificate information as important, epidemiologists certainly do. As one study noted, such errors

could cause "interference with accurate epidemiologic association between exposures or risks and various disease outcomes."[39]

Thus, it is apparent that although mortality statistics are often relied on by investigators, there may be little recognition that such data may contain inaccuracies. Accordingly, extreme caution is warranted in the evaluation of epidemiological studies using mortality data.

Comparisons in Lung Cancer Mortality Trends

One of the methods that have used to support the claim that "epidemic" increases in lung cancer are due to cigarette smoking has been to compare national and international trends in lung cancer mortality with cigarette consumption data. Again, however, such comparisons may be oversimplifications of the data and, therefore, not be reliable. They do not take into account, for example, that as the world's population has grown in size, life expectancy has generally increased markedly. This is significant because many diseases associated with smoking, including lung cancer, are also frequently diseases of old age.[40] Nor do they take into account the possible influence of changes over time in diagnostic and classification criteria for lung cancer and in coding rules for death certificates that make such trends suspect.

In general, the information on the cause of death recorded on death certificates in most countries is based on terminology from a coding system called the International Classification of Diseases (ICD). This system has been in effect for many years and, like many such classification systems, it has been and continues to be revised and changed. One of the most recent changes occurred in 1968 and had the very troubling effect of changing the lung cancer disease categories. Prior to that year, lung cancer had been separated into two categories -- lung cancer specified as primary and lung cancer unspecified as either primary or secondary, i.e., metastatic. In that year, however, these two categories were combined into a single classification.[41] Consequently, information obtained from death certificates before 1968 is not generally regarded to be comparable to the information obtained after 1968.[42] A professor of epidemiology has argued that this revision had the effect of "seriously" complicating attempts to trace the patterns of lung cancer in this century by "removing a needed safeguard for accuracy":

> Primary and secondary lung cancer are separate disease entities, with quite possibly distinct different causes. Since ten percent of all cancers spread to the lung, and since, for nearly twenty years, more deaths were coded in the unspecified than in the primary category, the combination of those two categories seriously confused the lung cancer data.[43]

Nonetheless, public health officials and cancer societies, in publicizing lung cancer mortality data, have combined the figures in both categories without any recognition that some or all the cases in the unspecified category may not have been primary lung cancer.[44] Additional changes in subsequent revisions of the ICD have also been criticized.[45] As one specialist commented, such changes are "a disturbing influence in the continuity of record-keeping and data-retrieval."[46]

Furthermore, some studies report significant differences among countries in the coding practices for cancer and death certificates. Such differences may, in part, explain variations in cancer mortality reported between countries. For example, researchers who reportedly found such differences among eight countries of the European Economic Community warned that "comparisons of mortality statistics for respiratory diseases between different countries should therefore be viewed with caution."[47] Similarly, another analysis of such differences asserted that "there is no doubt that such discrepancies explain part of the differences in cause-specific mortality between countries."[48]

Clearly, comparisons of national and international lung cancer mortality trends and cigarette consumption used to support the causal hypothesis are oversimplistic approaches to a complicated problem. Such an approach does not take into account

the numerous shortcomings of the data utilized. Without an appreciation of the difficulties involved, questionable conclusions may be drawn.

Lung Cancer in Women

Reports that lung cancer death rates have been rising rapidly for women are also used as "proof" that increased smoking is responsible. Once again, however, an analysis of the statistical data indicates that this simple assumption may be scientifically inaccurate. For example, the medical university group which suggested that "detection bias" may have distorted the statistical picture regarding cigarette smoking and lung cancer has argued that this may be particularly true for women. They reached that conclusion after observing a dramatic increase in the use of certain diagnostic techniques in female lung cancer patients -- from 52 percent of patients in 1953 to 78 percent by 1964.[49] They commented that their findings, which suggest that "the current increase of lung cancer in women may arise mainly from improved detection," also "evoke suspicions that cigarette smoking may lead more to the diagnosis of lung cancer than to the disease itself."[50]

In a related study, these researchers speculated that not only "detection bias" but also the increasing role of women in

the workplace may have a significant impact on the validity of lung cancer statistics:

> As women have increasingly entered the work force, they may have received an increased exposure to carcinogenic substances; but they have also received increased diagnostic surveillance from health programs associated with industrial employment.[51]

Thus, they suggest that even if the increase in women's lung cancer rates is real, other factors besides smoking may be responsible. This viewpoint has also been expressed by others. For example, a Canadian researcher remarked "much more significant than changes in women's smoking habits have been the changes in their employment."[52]

Other questions about the relationship between lung cancer and smoking in women were raised by a British medical physicist who carefully examined male and female lung cancer mortality patterns in England and Wales over the past century. He reported a "remarkable synchrony in the recorded changes" for both sexes during that time. In other words, even though male lung cancer rates in those countries have always been higher than female rates, the patterns of increase over time in both sexes have been almost exactly the same -- despite the fact that female consumption of cigarettes increased markedly thirty years after the striking rise in male consumption. In his view, if smoking caused this increased

mortality, the female lung cancer mortality pattern should not parallel the male pattern in time; rather, the female pattern should increase sharply about 30 years after the males'. However, he did not observe such differences. He specifically noted that "the most striking sustained rise in the increments of mortality for both sexes covers the period 1916-20 to 1931-35, when cigarette smoking can have made virtually no contribution to the large increase" in the female rate.[53]

As these examples illustrate, there are numerous difficulties in evaluating the epidemiological studies on smoking and lung cancer. Such difficulties raise serious questions regarding the reliability of the underlying data in such studies.

Biological Mechanism

Demonstration of a mechanism by which normal cells become cancerous is essential in addressing what role, if any, an agent plays in the development of cancer. Although hypotheses and theories frequently appear in the scientific literature, no biological mechanisms have been presented to explain how lung cancer is caused, whether by smoking or by any other factor. Indeed, two scientists have commented, "Although a large number of factors have been associated with the development of malignant neoplasms [cancers] in humans, the mechanisms involved are still largely

unknown."[54] Without knowledge of how a factor causes disease, one must conclude it is still a suspect, not an established cause.

Animal Studies

The results of laboratory studies and animal experiments also raise substantial questions about the nature of the relationship between smoking and lung cancer. Animal studies cited in this context have generally used one of two experimental techniques -- inhalation or skin painting. In inhalation studies, test animals are trained to or are forced to inhale cigarette smoke or one or more of its constituents. In skin painting studies, "tar" is painted on the shaved back or ears of test animals over prolonged periods of time. Both techniques are open to scientific criticism. Furthermore, despite the extensive use of these and other techniques, two well-known anti-smoking British researchers conceded that "30 years of laboratory research has yet to identify reliably the important carcinogenic factors in cigarette smoke."[55]

Inhalation Studies

Animal inhalation experiments are generally thought to provide the most relevant experimental data because such experiments come the closest to simulating the human smoking experience. Although many such experiments have been conducted, they have failed

to show that inhalation of fresh whole tobacco smoke causes human-type lung cancer in animals. This failure has been recognized in several U.S. Surgeon General's Reports on Smoking and Health. For example, the 1964 Report stated:

> The production of bronchogenic carcinomas [lung cancers] has not been reported by any investigator exposing experimental animals to tobacco smoke.[56]

A similar comment appeared in the 1982 Surgeon General's Report which was the most recent to focus on cancer:

> Attempts to induce significant numbers of bronchogenic carcinoma in laboratory animals were negative in spite of major efforts with several species and strains.[57]

The publication, several years later, of the results of a massive inhalation study using thousands of mice reaffirmed the conclusion of the 1982 report. According to the researchers who conducted the study, none of the smoke-exposed mice developed squamous cell carcinoma, the type of lung cancer most generally associated in the epidemiological studies with cigarette smoking. Although some of the animals did develop adenocarcinomas, a type of lung cancer not consistently associated with cigarette smoking, the same cancers occurred in the control animals; there was no statistically significant difference between the two groups.[58]

A few inhalation studies have reported the production of isolated lung cancers. One such experiment, using beagle dogs,[59] was widely publicized at one time as having provided the conclusive inhalation evidence. However, that study, like the other inhalation studies, has been heavily criticized for its improper experimental design, the experimental procedure followed, and possible misinterpretation of the pathological findings.[60]

Skin Painting Experiments

So-called skin painting experiments prompted a great deal of interest because the tumors which resulted are claimed to be evidence that similar tumors could develop in human lungs from inhaling cigarette smoke. However, it is not appropriate to compare skin painting experiments to the inhalation process of humans. Perhaps the most important reason is that "tar" is an artificially created laboratory product consisting of highly concentrated and physicially altered cigarette smoke particulate matter which is gathered either by passing cigarette smoke through a cold trap at extremely cold temperatures or by using filters and a drying process. The substances as found in "tar" are not found in cigarette smoke. That may be why this product is sometimes referred to as condensate.

In addition, the concentrations of "tar" used in such experiments are extremely high. One researcher has estimated the amounts utilized to be equivalent to an individual smoking over 100,000 cigarettes per day.[61] Furthermore, the skin and ears of laboratory animals are not similar to human lung tissue. Animal skin lacks the intricate clearance mechanisms of the lungs, such as the mucus blanket which coats the lining of the major airways of the lung. Consequently, such experiments have been characterized as applying "the wrong material, in the wrong form, in the wrong concentration, to the wrong tissue of the wrong animal."[62]

Thus, the animal studies designed to investigate the claimed relationship between smoking and lung cancer do not support either the popular interpretation of the epidemiological evidence or a conclusion of causation. As a knowledgeable observer of research in this area has stated: "Bronchogenic carcinoma has never been produced by tobacco or its products in any experimental animal despite the multiplicity of attempts."[63] [Emphasis added] In short, animal studies do not support the claim that cigarette smoking causes lung cancer.

Other Factors

Lung cancer is said to be multifactorial in etiology. That is, many factors may be involved in the development of lung

cancer. For example, in addition to smoking, occupational exposures,[64] viruses,[65] diet,[66] genetic influences,[67] food additives,[68] pollution,[69] depression and stress,[70] impaired body defense mechanisms,[71] diesel and gasoline exhausts,[72] and even keeping pet birds[73] have been implicated as risk factors.

Occupational exposures in particular have received a great deal of attention as a possible factor in lung cancer development. In fact, researchers with the International Agency for Research on Cancer (IARC) attempted to estimate the fraction of lung cancer cases which may be attributable to occupational exposures. Although they determined that the available published literature is too limited to make such estimates for the general public, they did conclude that the proportion of cases attributable to such exposures "can be very elevated (up to 40%) among selected populations resident in specific areas." In making these estimates, they attempted to take into account the alleged impact of cigarette smoking but concluded that it "does not appear to act consistently as a strong confounder of the association between lung cancer and elevated risks due to the exposure to carcinogens [cancer causing substances] in the working environment."[74]

Despite such reports, many workers are still exposed to industrial agents for which no occupational exposure standards have been established. This problem was recognized by one of the

leading authorities on occupational cancer, who warned that such exposures could continue if public attention was concentrated too strongly on cigarette smoking.[75] His concerns are shared by others, including an expert in environmental contaminants who has studied these problems for many years:

> A real question exists if cigarette smoking is not diverting attention from the effects of occupational exposure on industrial workers . . . .[76]

He contends that when both smoking and occupation are considered "it is the occupation -- and not smoking -- that appears to be the major cause of cancer."[77]

Other theories have also been advanced. In the 1950's, the late Sir Ronald Fisher of England, world-famed statistician and geneticist, proposed that "constitutional" factors might be far more important than smoking in lung cancer development.[78] His hypothesis suggests that some people who have a hereditary predisposition for lung cancer also have a hereditary tendency toward smoking. More recently, a prominent medical physicist, who reviewed much of the literature on smoking and lung cancer, concluded that Fisher's hypothesis still provides the best explanation of the data.[79]

In the past few years, another factor has received considerable attention. Radon is a naturally occurring radioactive gas formed by the disintegration of uranium in the soil. Surveys have shown that indoor concentrations of radon gas and its decay products can be appreciable. Based on studies of uranium miners exposed to radon daughters, it has been asserted that radon may be a significant health risk for residents of homes located in areas with high concentrations of uranium. In the United States, for example, it has been estimated that about 20,000 lung cancer deaths a year may be attributed to radon.[80] In the United Kingdom, about 5,000 mostly lung cancer deaths are attributed to radon.[81]

However, which -- if any -- of these factors plays a role in the causation of lung cancer is as yet undetermined.

Conclusion

Despite claims about smoking and lung cancer, it has not been scientifically established that smoking causes lung cancer. The pathogenesis or development of lung cancer is complex, and an understanding of lung cancer causation continues to elude the scientific community. Basic issues remain unresolved, and much more research is needed to fill the wide gaps in knowledge.

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LUNG CANCER:

CLAIMS/RESPONSES

CLAIM: The statistical evidence against smoking is so strong that no doubt remains about its harmful effect on health.

RESPONSE: One thing that can be said for certain about smoking is that it produces statistics. But, as many have emphasized, statistics can be used to "prove" just about anything. However, statistical associations alone can never prove cause-and-effect relationships; they simply provide leads for further research.[1]

In addition, the statistical studies on smoking and health have been challenged scientifically. Many of the population studies from which those statistical associations are reported have been criticized as being seriously flawed in their methodology and reliability of information. For example, many have relied on death certificates for information on causes of death, but numerous studies have reported that death certificates contain inaccurate information.[2] Such errors can arise where, for example, an individual is diagnosed as having lung cancer but at autopsy is found to have had a primary cancer in another site, for example the kidney, that metastasized or spread to the lung. If the death

certificate is not revised to reflect the results of the autopsy but instead retains the initial diagnosis, which has been shown to occur, then that incorrect information will be used in future studies.

Furthermore, many of these statistical studies have failed to take into account numerous other factors that have been associated with lung cancer in addition to smoking, such as lifestyle, genetic and inherited traits, occupational and environmental exposures, and psychological variables.[3]

Finally, the reported "epidemic" of deaths attributed to smoking may be in part artifactual and misleading. Because diagnostic techniques have greatly improved over the last 50 years with the development of such tools as the x-ray and the bronchoscopy, many cases of diseases such as lung cancer are diagnosed today which were either missed or misdiagnosed earlier.[4] Thus, the "epidemic" may reflect dramatic medical progress. As the world's population grows in size, life expectancy has generally increased markedly. This is significant because many diseases associated with smoking are also frequently diseases of old age.

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CLAIM: Smoking causes lung cancer.

RESPONSE: This is a misstatement. How can people claim that it has been proven that smoking causes lung cancer when science has not determined the mechanism by which a normal lung cell becomes cancerous?[1] Without this scientific understanding, this claim must be viewed as just that, a claim or conjecture -- not an established fact.

There is a statistical association between smoking and lung cancer, but even the first U.S. Surgeon General's Report conceded that statistical associations alone cannot prove a causal relationship.[2] Yet much of the existing data cited in support of a causal relationship between smoking and lung cancer is, in fact, based on statistical studies.

Moreover, eminent scientists have questioned the data on smoking and lung cancer because of its many inconsistencies and its failure to answer such basic questions as:

-- Why do the vast majority of "heavy smokers" in any study never develop lung cancer?[3] On the other

hand, why do a significant percentage of nonsmokers get lung cancer?[4]

-- Why don't lung cancer rates in countries such as Japan parallel cigarette consumption? In several countries, tobacco consumption is high but the rate of lung cancer is low or vice versa.[5]

Cancer is a very complex disease. Many other factors have been associated with this disease in addition to smoking, including occupational and environmental exposures, diet, viruses, heredity, and stress.[6] Clearly there are many gaps in knowledge about lung cancer that only further research will resolve.

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CLAIM: Lung cancer is a smoker's disease.

RESPONSE: This is simply not the case. Studies have reported finding a significant number of lung cancers among non-smokers.[1] Furthermore, not only were cases of lung cancer reported long before cigarette smoking came into popular use,[2] but also the vast majority of "heavy" cigarette smokers in the studies do not develop lung cancer.[3]

In addition, lung cancer is multi-factorial in etiology or causation. That is, many factors may be involved in the development of lung cancer. For example, in addition to smoking, occupational exposures, viruses, diet, genetic influences, food additives, pollution, stress, aging, impaired body defense mechanisms, and diesel and gas exhaust are just a few of the many risk factors that have been suggested in connection with lung cancer.[4]

Which -- if any -- of these factors plays a role in the causation of lung cancers is as of yet undetermined.

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CLAIM: Tests on laboratory animals have proven that cigarette smoke causes lung cancer.

RESPONSE: A review of the literature demonstrates that this statement is inaccurate. Even the 1982 U.S. Surgeon General's Report, which was the most recent to focus on cancer, conceded that attempts to induce significant numbers of lung cancer in laboratory animals have been negative.[1]

People who make such statements are generally referring either to inhalation or skin painting experiments. However, as the Surgeon General's Report statement suggests, such techniques have been unsuccessful.

For example, although many inhalation experiments have been conducted, they have failed to show that inhalation of fresh, whole tobacco smoke causes human-type lung cancer in animals.[2] A few inhalation studies have reported the production of isolated lung cancers, but these studies have been heavily criticized for improper experimental design, the experimental procedure followed, and possible misinterpretation of the pathological findings.[3]

So-called skin painting experiments also have been heavily criticized for numerous reasons. These include the fact that the substances found in "tar," which is an artificially obtained laboratory product that is painted on the skins of animals in these experiments, are not found in tobacco smoke. In addition, the concentrations of "tar" used in such experiments have been extremely high. Furthermore, the skin and ears of laboratory animals are not similar to human lung tissue. Consequently, such experiments have been appropriately characterized as applying the wrong material, in the wrong form, in the wrong concentration, to the wrong tissue of the wrong animal.[4]

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Second Congress, Second Session, 97-123, February 1, 3, and 10, 1972.

CIGARETTE INGREDIENTS

CAVEAT: The information contained in this paper regarding the use of non-tobacco ingredients in cigarettes is based primarily on information obtained from, and the experience of, cigarette manufacturers in the United States. To the extent that statements regarding the use of non-tobacco ingredients in cigarettes and other tobacco products may be made based on information contained in this paper, be advised that the number, quantity, and type of non-tobacco ingredients added to cigarettes in other parts of the world, and the specific identity of such non-tobacco ingredients, may not correspond to the use and experience of American manufacturers as described in this paper.

INTRODUCTION

Non-tobacco ingredients are used in the manufacture of cigarettes and other tobacco products for a variety of reasons. For example, these ingredients improve the balance of smoke in terms of taste, flavor, or burning characteristics. Such substances have been added to tobacco since the American Indians introduced smoking to European explorers. In addition, many ingredients added to tobacco also occur naturally in tobacco, such as sugar.

The extent to which non-tobacco ingredients are used to improve properties of tobacco products has varied considerably from country to country and time to time. For example, the "All Virginia" cigarettes of the United Kingdom and the traditional dark, air-cured cigarettes of France made minimal use of non-tobacco ingredients. In contrast, "American-style" cigarettes have generally utilized a wide variety of such substances. Today, however, non-tobacco ingredients are used in the manufacture of virtually all tobacco products throughout the world, including "Virginia" cigarettes.

Non-tobacco ingredients generally fall into four categories -- flavorings, casing materials, humectants, and processing aids. The majority of the ingredients utilized are flavorings which are used to enhance the taste and refine the smoking qualities of cigarettes. As such, flavorings are an

integral part of tobacco products. They contribute to the overall impression of the product through their effect on the taste of smoke and the smell of the cigarettes. Flavorings make the major contribution to the distinctive taste and aroma of the many individual brands and styles of cigarettes.

Flavorings are generally natural components, such as menthol, spices, and citrus, or synthetics that have been developed to provide the flavor and aroma characteristic of natural materials. Menthol is probably the best known ingredient added to tobacco in cigarettes as a flavoring.

In addition to flavorings, cigarettes also contain casing materials. The precise ingredients used to achieve these desired results depend upon the style of the tobacco product involved in terms of both the tobacco used and delivery constraints which must be achieved. For example, traditional "Virginia" cigarettes contain natural sugars while light air-cured tobaccos (which comprise a significant part of blended cigarettes) have negligible levels. Treatment of these air-cured tobaccos with quantities of sugars and other materials in the form of a "casing" is necessary to develop their character and make for smoother smoke.

Humectants and moisturizers, such as glycerol or propylene glycol, are also used in the manufacture of cigarettes

throughout the world. Humectants help to stabilize the tobacco moisture content and smoking properties that may result from fluctuations in temperature and humidity. The need for these ingredients varies both with product type and the circumstances in which the product is marketed.

Finally, processing aids, such as carbon dioxide, are used for a variety of purposes, including the adjustment of nicotine levels in tobacco, which varies from crop to crop, and the expansion or "puffing" tobacco in the production of lower "tar" and nicotine brands. Processing aids are present in finished cigarettes in trace quantities, if at all.

SUBSTANCES USED IN TOBACCO MANUFACTURING ARE ALSO USED IN OTHER PRODUCTS

Most of the ingredients used in cigarettes have a long history of use in foods, confections, and beverages and have been reviewed for use in these products by a variety of governmental agencies. For example, most non-tobacco ingredients used in cigarettes manufactured in the United States are included in the lists of substances "Generally Recognized as Safe" (GRAS) as determined by the U.S. Food & Drug Administration (FDA) and by the U.S. Flavor and Extract Manufacturers Association (FEMA).

AMOUNTS OF NON-TOBACCO INGREDIENTS ADDED TO CIGARETTES

The amount of ingredients incorporated into tobacco products vary by weight from a few percent, e.g., casings (such as sugars, cocoa, licorice extract, etc.) and humectants (glycerol, propylene glycol, etc.) used traditionally in blended cigarettes, down to even smaller amounts of flavorings. Flavor substances similar to those used in the manufacture of food and drink, or identical to those found in tobacco itself, are used as "top flavors" in very small amounts. "Top flavors" help give cigarette brands their distinctive taste and aroma and, in the aggregate, normally constitute less than one tenth of one percent by weight of the final product.

A small number of casing materials, moisturizers and major flavorings account for the great bulk of ingredients actually in a cigarette. Approximately 25 substances (casings, humectants, and processing aids) comprise over 99% of the total amount, by weight, of non-tobacco ingredients used in the manufacture of cigarettes in the United States. As noted, any ingredients used as processing aids (e.g., carbon dioxide) in a finished cigarette are present only in trace quantities, if at all.

REGULATION OF CIGARETTE INGREDIENTS

The identities of specific ingredients used in cigarettes and the mixture of ingredients comprising the recipe for any individual brand are closely-guarded trade secrets of the manufacturer. These ingredients make major contributions to the taste and appeal of individual brands. Disclosure of the ingredients used in cigarette manufacture could reveal product formulas that have required years of research to develop and cause irreparable damage to the manufacturer in a highly competitive industry. Although a wide range of ingredients used in tobacco products have been listed with governmental agencies and mentioned in other publications, specific recipes are closely-guarded trade secrets.

The issue of the addition of non-tobacco ingredients to tobacco products developed in part as a parallel response to regulatory activities in other areas such as food additives. Historically, regulation of tobacco ingredients has been a response to interest expressed in some countries over possible adulteration of consumer products in general.

Governmental bodies in several countries, including Great Britain, Canada, and Germany, have reviewed and approved, a large

number of non-tobacco ingredients for use in cigarettes. For example, in 1973 the Independent Scientific Committee on Smoking and Health ("ISCSH") was set up in the Great Britain in order to advise the British government on scientific aspects of matters concerning smoking and health, and, in particular, to compile lists (known as the "ISCSH" lists) of allowed and prohibited additives to tobacco products. Non-tobacco ingredients approved for use in tobacco products were those "a) for which after long-term usage no evidence has emerged of their harmful effect (long-term being defined as in constant use for 20 years or more); or b) for which the results of toxicity testing by a manufacturer have been reported to, and have satisfied, the Committee."[1] The ISCSH was charged with specifically prohibiting the use of non-tobacco ingredients which on pyrolysis (or burning) might, in the ISCSH's view, produce a potential or known health risk or for which the results of toxicity testing have not satisfied the ISCSH.

Any company proposing to market a cigarette in Great Britain containing non-tobacco ingredients must abide by the ISCSH guidelines in all respects. The ISCSH periodically reviews and updates its lists and considers its system to "work well."[2] According to the fourth and most recent report of the ISCSH, "The Committee will continue to ensure the safety of additives used in all smoked tobacco products."[3]

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Other governmental bodies also maintain lists of substances that may not be added to cigarettes. For example, German ordinances specifically prohibit the use of certain substances as ingredients in tobacco products which, in general, were determined to be harmful as food additives. Manufacture or import of cigarettes containing such ingredients is prohibited in Germany.

Since 1986, the six major cigarette manufacturers in the United States have annually provided the U.S. Department of Health and Human Services (DHHS) with lists of non-tobacco ingredients added to tobacco in the manufacture of cigarettes in the United States. These lists have been submitted pursuant to the requirements of the 1984 Federal Cigarette Labeling and Advertising Act. The DHHS is required to review the lists and prepare a report to the U.S. Congress on the health effects, if any, associated with the use of those ingredients. To date, five yearly lists have been submitted, although no report has been issued from the DHHS.[4] Non-tobacco ingredients used in cigarette filters and paper are not included in the United States submissions. The German and Great Britain (ISCSH) lists, however, also regulate the use of non-tobacco ingredients in cigarette filters and paper.

Legislation regulating non-tobacco ingredients has been slow to develop outside Europe. The absence of such legislation may well reflect the lack of any convincing evidence that the use

of non-tobacco ingredients in cigarettes and other tobacco products has any deleterious effects on consumers.

CLAIMS CONCERNING HEALTH RISKS

Cigarette manufacturers and various government agencies have tested the major use ingredients through various bioassays such as the "Ames" test and, in some cases, have conducted animal studies of individual ingredients and combinations of ingredients. These tests typically involve two, five, or even 10 times or more than the amount of the ingredient used in a commercial cigarette. None of these studies indicate that the use of ingredients in cigarettes cause disease in smokers. Moreover, none of the substances currently used by the six major United States cigarette manufacturers are considered potential carcinogens by the National Toxicology Program (NTP), the International Agency for Research on Cancer (IARC) or any other recognized organization which evaluates the toxicity of substances.

Furthermore, 19 of the 25 ingredients that comprise over 99% of the total amount, by weight, of the non-tobacco substances added to tobacco in cigarettes manufactured or sold in the U.S. are listed as "Generally Recognized as Safe" (GRAS) or otherwise approved for use as food additives by FEMA or the FDA. Twenty are approved by Great Britain's ISCSH for use in cigarettes at

prescribed levels. None are prohibited for use in cigarettes by any government ordinance.

LEGISLATIVE CONSIDERATIONS

Legislation regarding the use of ingredients in tobacco products creates a number of potential consequences which must be considered. Under some circumstances, such regulation could lead to restrictions on trade where it is particularly disadvantageous to one or another product type. Moreover, as noted earlier, disclosure of non-tobacco ingredients themselves presents a difficult issue, particularly with regard to recipes which may consist of complex, proprietary formulations developed and maintained as trade secrets by manufacturers in the tobacco industry, as well as the food and beverage industry. For example, the ingredient lists submitted to the DHHS are subject to strict confidentiality requirements which prevent their release or disclosure to the public or media and restrict the distribution of the list within the Department.[5]

Tobacco manufacturers and their suppliers fully understand the need to carefully monitor the materials used in their products and, in fact, maintain continuing review. There is no compelling evidence that indicates that the imposition of legislation or regulation in this area has any additional consumer benefit.

REFERENCES

1. Department of Health and Social Security, Northern Ireland Office, Scottish Home and Health Department, Welsh Office, First Report of the Independent Scientific Committee on Smoking and Health: Tobacco Substitutes and Additives in Tobacco Products, London, Her Majesty's Stationery Office, 1-29 (at 28), 1975.

2. Department of Health and Social Security, Department of Health and Social Services, Northern Ireland, Scottish Home and Health Department, Welsh Office, Fourth Report of the Independent Scientific Committee on Smoking & Health, London, Her Majesty's Stationery Office, 1-68 (at 26), 1988.

3. Department of Health and Social Security, Department of Health and Social Services, Northern Ireland, Scottish Home and Health Department, Welsh Office, Fourth Report of the Independent Scientific Committee on Smoking & Health, London, Her Majesty's Stationery Office, 1-68 (at 26), 1988.

4. Whitley, C.O., Statement, Re: "Tobacco Control and Health Protection Act." During: Hearings Before the Committee on Energy and Commerce, Subcommittee on Health and the Environment, 1-44, July 12, 1990.

5. Federal Cigarette Labeling and Advertising Act, Pub. L. No. 98--474, 98 Stat. 2204 (1984).

INGREDIENTS

CLAIMS/RESPONSES

CLAIM: Cigarette manufacturers add harmful substances to tobacco when they make cigarettes that they don't want to tell the public about.

RESPONSE: In some countries, substances generally called "ingredients" are added to tobacco, for example, to improve its flavor, taste, or burning characteristics. Consequently, these substances make major contributions to the distinct flavor and aroma of individual brands and types of cigarettes.

Most of these substances have a long history of use in foods, confections, and beverages and have been reviewed for use in these products by a variety of governmental agencies such as the Food and Drug Administration in the United States.

Since these ingredients make major contributions to the taste and appeal of individual brands, manufacturers are naturally concerned about revealing the identities of specific ingredients used in cigarettes and the mixture of ingredients comprising the recipe for any individual brand. Such disclosure could reveal product formulas that have required years of research to develop and could

cause irreparable damage to the manufacturer in a highly competitive industry. Although a wide range of ingredients used in tobacco products have been listed with governmental agencies and mentioned in other publications, specific recipes have the highest commercial value and are closely guarded trade secrets.

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CLAIM: Cigarette ingredients should be regulated.

RESPONSE: Governmental bodies in several countries, including Great Britain and Germany, already review and approve a large number of non-tobacco ingredients for use in cigarettes. In Great Britain, for example, the Independent Scientific Committee on Smoking and Health ("ISCSH") was set up in order to advise the British government on scientific aspects of matters concerning smoking and health and, in particular, to compile lists of allowable and prohibited ingredients to tobacco products. Non-tobacco ingredients approved for use by the ISCSH must meet certain criteria regarding safety and health.

Other governmental bodies also maintain lists of substances that may not be added to cigarettes. For example, German ordinances specifically prohibit the use of certain substances as ingredients in tobacco products where, in general, these substances were determined to be harmful as food additives. Manufacture or import of cigarettes containing listed ingredients is prohibited in that country. In the United States, the six major cigarette manufacturers have been required since 1986 to provide the United States Department of Health and Human Services (DHHS) with annual lists of non-tobacco

ingredients added to tobacco in the manufacture of cigarettes in that country. The DHHS is required to review the lists and submit a report to the U.S. Congress on the health effects, if any, associated with the use of those ingredients. To date, lists for five years have been submitted, but no report has been issued by the DHHS.

CLAIM: Non-tobacco ingredients in cigarettes are harmful to the smoker.

RESPONSE: Many of the ingredients that comprise the large bulk of non-tobacco ingredients added to tobacco in cigarettes in, for example, the United States, Great Britain, and Germany are either on lists approved for use as food additives or are approved or disapproved for use by specific government ordinances. Cigarette manufacturers and various government agencies have tested those ingredients used most often through various bioassays and, in some cases, have conducted animal studies of individual ingredients and combinations of ingredients. These studies typically involve two, five, or even 10 times or more the amount of the ingredient used in a commercial cigarette. Such studies have not shown that the use of ingredients in cigarettes causes disease in smokers.